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(54) Title: A PROCESS FOR THE PREPARATION OF SUBSTITITED PYRIDINYLMETHYLSULFINYL- BENZIMIDAZOLE ENANTIOMERS

(57) Abstract: The present invention provides an enantioselective process for preparing substituted benzimidazoles either as a single enantiomer or in an enantiomerically enriched form.

A PROCESS FOR THE PREPARATION OF SUBSTITUTED PYRIDINYLMETHYLSULFINYL-BENZAMIDE ENANTIOMERS

FIELD OF THE INVENTION

The present invention relates to an enantioselective process for preparing substituted benzimidazoles either as a single enantiomer or in an enantiomerically enriched form and novel intermediates useful for preparing the substituted benzimidazoles.

BACKGROUND OF THE INVENTION

Substiituted 2-((4-alkoxy-2-pyridinyl)methylsulfinyl)-1H-benzimidazoles such as for example omeprazole, pantoprazole, lansoprazole and rabeprazole including their stereioisomers are inhibitors of gastric acid secretion. Omeprazole, chemically 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole is for instant disclosed in EP 124496.

These compounds and structurally related compounds have a stereogenic center at sulfur and therefore exist as two optical isomers. The resolution processes of racemates of these compounds were for example disclosed in DE 4035455 and WO 94/27988. According to these processes racernic compound is converted to a diastereomeric mixture, diastereomers are separated and desired isomer is liberated from a separated diastereomer.

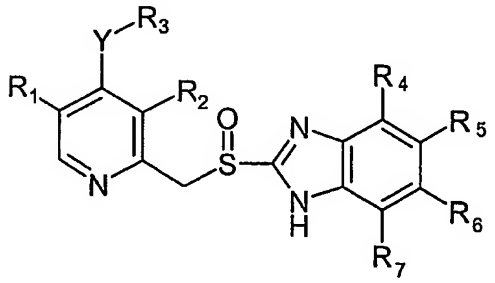
The resolution process involves additional resolution steps and a waste of material in the form of undesired diasteriomer.

Enantioselective synthesis is described for example in Euro. J. Biochem. 166 (1987) 453 and US 5,948,789. Disadvantages of these methods are that strict control of conditions is to be maintained and strict control of quantities of oxidizing agents is required for avoiding oxidation of desired sulfoxide to sulfone impurity. Moreover, the crystallization from the reaction mixture of a stereoisomer of the sulfoxide is difficult.

We have discovered a novel process for preparation of enantiomers of the sustituted benzimidazoles; and the novel process solve the problems associated with the prior art processes for preparing these and related compounds.

DESCRIPTION OF THE INVENTION

The present invention provides a novel process for preparing a sulfoxide of formula I either as a single enantiomer or in an enantiomerically enriched form:



---------- I

Wherein

R_1 and R_2 are same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, phenylalkyl and phenylalkoxy;

R_3 is alkyl optionally substituted by fluorine, alkoxyalkyl and phenylalkyl;

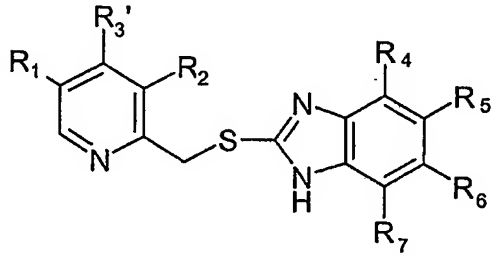
Y is O or S

and

R_4, R_5, R_6 and R_7 are same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl and trifluoroalkyl;

which process comprises the steps of:

a) an asymmetric oxidation in an organic solvent of a prochiral sulfide of the formula II



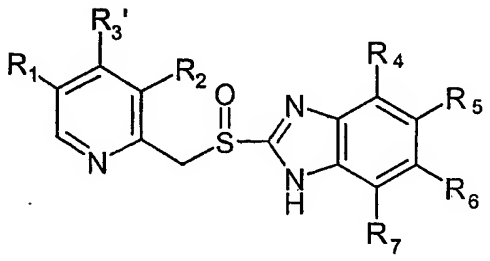
---------- II

Wherein R_1, R_2, R_4, R_5, R_6 and R_7 are as defined above and R'_3 is halo or nitro

with an oxidizing agent and a chiral titanium complex;

and

b) reaction of the compound obtained either as a single enantiomer or in an enantiomerically enriched form in the step (a) of formula III:



---------- III

wherein R_1, R_2, R_3', R_4, R_5, R_6 and R_7 are as define for formula II;

with a compound of formula IV:

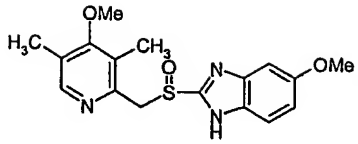
$((R_3\text{-}Y))_n M$

wherein R_3 and Y are as defined for formula I, M is alkali metal or alkaline earth metal and n is 1 when M is alkali metal and n is 2 when M is alkaline earth metal;

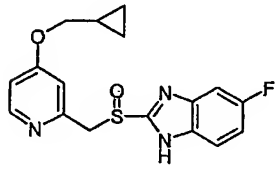
to obtain a compound of formula I either as a single enantiomer or in an enantiomerically enriched form.

Alkyl defined above refers to branched or straight C1 to C9 alkyl and may also represent cycloalkylalkyl group. Alkoxy defined above refers to branched or straight C1 to C9 alkoxy and may also represent cycloalkylalkoxy.

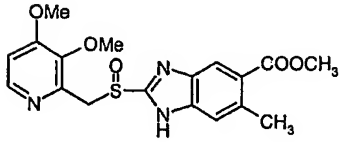
Preferably, the sulfoxides prepared by the novel method are sulfoxides of formula Ia to If either as a single enantiomer or in an enantiomerically enriched form:



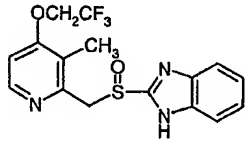
Ia



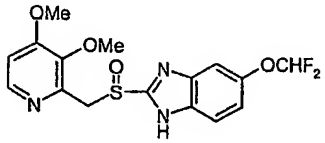
Ib



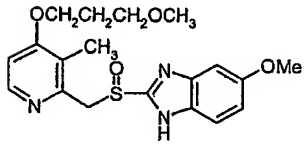
Ic



Id



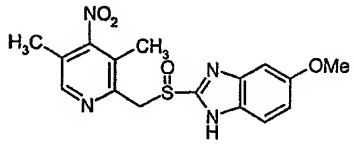
Ie



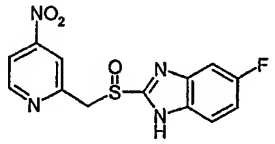
If

The compounds defined by the above formulas I, Ia to If may be converted to pharmaceutically acceptable salts thereof by conventional methods.

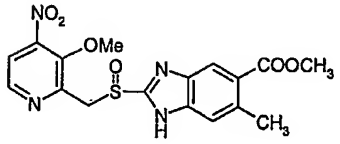
The preferred compounds of the formula III are the compounds of the formula IIIa to IIIf either as a single isomer or in an enantiomerically enriched form:



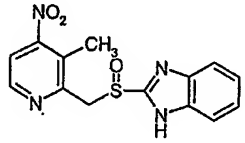
---------- IIIa



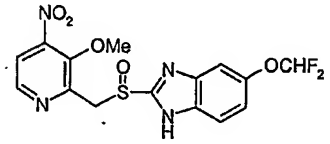
---------- IIIb



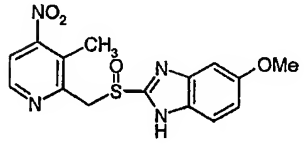
---------- IIIc



---------- IIId



---------- IIIe



---------- IIIf

The asymmetric oxidation in step (a) can be carried out by mixing chiral titanium complex with the prochiral sulfide. The enantioselective oxidation can also be carried out by preparing chiral titanium complex in the presence of prochiral sulfide.

The oxidation gives the product of the formula III in enantiomeric excess (ee) of at least 40%, usually above 90%.

Single enantiomers or enantiomerically enriched forms of the compounds of formula III are novel.

The asymmetric oxidation is carried out in an organic solvent. Examples of the suitable solvents are carboxylates such as ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate; alcohols such as methanol, ethanol and isopropyl alcohol; acetonitrile; tetrahydrofuran; dimethylformamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as methylene dichloride, chloroform, carbontetrachloride, ethylene dichloride, etc.; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone etc.; ethers such as tert-butyl methyl ether, diethyl ether; and diethyl carbonate. A mixture of the solvents may also be used. Preferred organic solvents are ethyl acetate, tetra hydrofuran, toluene, methyl ethyl ketone, methyl isobutyl ketone, methylene dichloride, tert-butyl methyl ether and diethyl carbonate.

The titanium complex is prepared from a chiral ligand and a titanium IV compound such as titanium (IV) alkoxide. Preferable titanium (IV) alkoxide is titanium (IV) isopropoxide or titanium (IV) propoxide.

The amount of titanium complex is not critical. An amount of about 0.02 to 10.00 equivalents may be used, 0.1 to 5.0 equivalents being more preferable.

The titanium complex can also be prepared by reaction of titanium tetrachloride with a chiral ligand in the presence of a base.

An oxidizing agent suitable for the asymmetric oxidation is preferably a hydroperoxide such as tert-butylhydroperoxide or cumene hydroperoxide.

The chiral ligand used in the preparation of the titanium complex is preferably a chiral alcohol such as esters of tartaric acids. More preferable esters are (-)-diethyl D-tartrate and (+)-diethyl L-tartrate.

The oxidation is preferably carried out in the presence of a base. The preferable bases are alkyl amines such as triethylamine, diisopropylethylamine, pyridine, morpholine and N-methyl morpholine.

The oxidation may also be carried out in the presence of water along with the organic solvent.

The compounds of the formula III can be isolated from the reaction mixture conveniently as solids and can be used in the next step. The reaction mixture can also be used directly in the next step.

In the step (b), the reaction of the compound of formula III with the compound of formula IV is carried out in a solvent or a mixture of solvents. Preferred solvents are carboxylates such as ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate; alcohols such as methanol, ethanol and isopropyl alcohol; acetonitrile; tetrahydrofuran; dimethylformamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as methylene dichloride, chloroform, carbontetrachloride, ethylene dichloride, etc.; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone etc.; ethers such as tert-butyl methyl ether, diethyl ether; and diethyl carbonate. A mixture of the solvents may also be used. More preferable organic solvents are ethyl acetate, tetrahydrofuran, toluene, methyl ethyl ketone, methyl isobutyl ketone, methylene dichloride, tert-butyl methyl ether and diethyl carbonate.

No racemization is found to occur during the substitution reaction.

Compounds of formula IV wherein M is sodium or potassium is preferred.

The substitution reaction is carried out below the boiling temperature of the solvent/solvents used, preferably at about -40^0C to boiling temperature of the solvents and more preferably at about 0 to 40^0C.

The quantity of the compound of the formula IV is not critical, but atleast 1 equivalent of the compound of the formula IV is required for better yield.

The starting compounds of the formula II and IV are known or can be obtained from known processes.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope or spirit of the invention.

Example 1

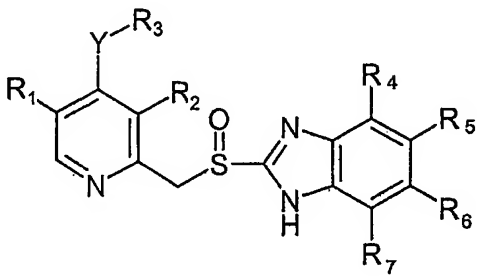
5-Methoxy-2-[[(3,5-dimethyl-4-nitro-2-pyridinyl)methyl]thio]-1H-benzimidazole (25 gm), ethyl acetate (250 ml) and water (0.5 ml) are mixed and the contents are heated to 35°C. (-)-Diethyl D-tartrate (22.7 gm) and titanium isopropoxide (20.45 gm) are added, the contents are stirred for 1 hour at 35°C and cool to 25°C. N,N-Diisopropyl ethylamine (11.7 gm) is added to the reaction mass and to the clear solution formed cumene hydroperoxide (26.5 gm) is added slowly to the solution at 25°C in 15 minutes. The reaction mass is heated to 35°C and maintained for 12 hours. Isooctane (20 ml) is added to the reaction mass and extracted with 12% ammonia solution (200 ml) and adjusted the pH of the aqueous layer to 7 to 7.5 with acetic acid at 20°C. Then extract the aqueous solution with ethyl acetate (250 ml), dried and distilled off ethyl acetate. The residue obtained is dissolved in acetonitrile (50 ml) at 70°C and cooled to 0°C. (S)-5-Methoxy-2-[[(3,5-dimethyl-4-nitro-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (ee: 95%) obtained as solid is collected by filtration.

Example 2

(S)-5-Methoxy-2-[[(3,5-dimethyl-4-nitro-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (ee: 95%, 10 gm) is mixed with methanol (100 ml) and the contents are cooled to 10°C. Sodium methoxide solution (20 ml, 30% in methanol) is added and heated to 50°C. The contents are maintained at this temperature for 3 hours, cooled to 25°C and water (100 ml) is added. The pH of the reaction mass is adjusted to 8.0 with acetic acid. Then the reaction mass is extracted with methylene dichloride (100 ml), the layers are separated and the methylene dichloride layer is washed with water (100 ml). Methylene dichloride layer is dried with sodium sulfate, methylene dichloride solvent is distilled off to obtain (S)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as residue. The residue is dissolved in methanol (30 ml), cooled to 10°C and then potassium hydroxide (1.5 gm) in methanol (10 ml) is added slowly for 15 minutes. The reaction mass is stirred for 12 hours and the solid obtained is filtered to obtain potassium salt of (S)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (ee: 95%).

We claim:

1) A process for the preparation of a sulfoxide of formula I either as a single enantiomer or in an enantiomerically enriched form:



---------- I

Wherein

R_1 and R_2 are same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, phenylalkyl and phenylalkoxy;

R_3 is alkyl optionally substituted by fluorine, alkoxyalkyl and phenylalkyl;

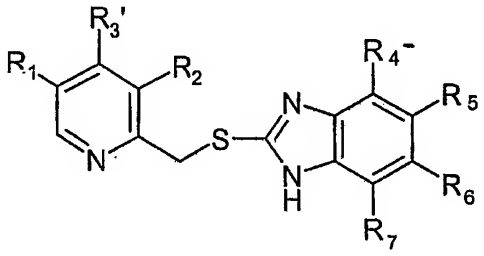
Y is O or S

and

R_4, R_5, R_6 and R_7 are same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl and trifluoroalkyl;

which process comprises the steps of:

a) an asymmetric oxidation in an organic solvent of a prochiral sulfide of the formula II



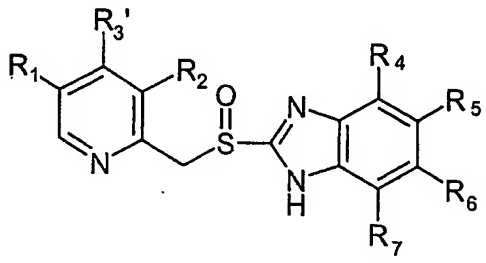
---------- II

Wherein R_1, R_2, R_4, R_5, R_6 and R_7 are as defined above and R'_3 is halo or nitro

with an oxidizing agent and a chiral titanium complex;

and

b) reaction of the compound obtained either as a single enantiomer or in an enantiomerically enriched form in the step (a) of formula III:



---------- III

wherein R_1, R_2, R_3', R_4, R_5, R_6 and R_7 are as define for formula II;

with a compound of formula IV:

$((R_3\text{-}Y))_n M$

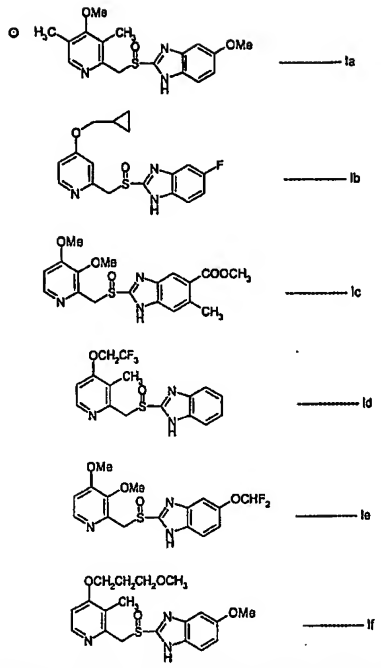
wherein R_3 and Y are as defined for formula I, M is alkali metal or alkaline earth metal and n is 1 when M is alkali metal and n is 2 when M is alkaline earth metal;

to obtain a compound of formula I either as a single enantiomer or in an enantiomerically enriched form.

2) A process according to claim 1, wherein the compound of the formula III obtained is single enantiomer.

3) A process according to claim 1, wherein the compound of the formula III obtained is in enantiomerically enriched form.

4) A process according to claim 1, wherein the compounds of the formula I prepared are sulfoxides of formula Ia to If either as a single enantiomer or in an enantiomerically enriched form:



5) A process according to claim 1, wherein the asymmetric oxidation is carried out by mixing chiral titanium complex with the sulfide of formula II as defined in claim 1.

6) A process according to claim 1, wherein the asymmetric oxidation is carried out by preparing chiral titanium complex in the presence of prochiral sulfide.

7) A process according to claim 1, wherein the organic solvent is selected from the group consisting of carboxylates such as ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate; alcohols such as methanol, ethanol and isopropyl alcohol; acetonitrile; tetrahydrofuran; dimethylformamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as methylene dichloride, chloroform, carbontetrachloride, ethylene dichloride, etc.; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone etc.; ethers such as tert-butyl methyl ether, diethyl ether; and diethyl carbonate.

8) A process according to claim 7, wherein the organic solvent is selected from ethyl acetate, tetrahydrofuran, toluene, methyl ethyl ketone, methyl isobutyl ketone, methylene dichloride, tert-butyl methyl ether and diethyl carbonate.

9) A process according to claim 1, wherein the titanium IV compound is titanium (IV) alkoxide.

10) A process according to claim 9, wherein the titanium (IV) alkoxide is titanium (IV) isopropoxide or titanium (IV) propoxide.

11) A process according to claim 1, wherein the amount of titanium complex used is about 0.02 to 10.00 equivalents.

12) A process according to claim 11, wherein the amount of titanium complex is about 0.1 to 5.0 equivalents.

13) A process according to claim 1, wherein the oxidizing agent is hydroperoxide.

14) A process according to claim 13, wherein the hydroperoxide is cumene hydroperoxide.

15) A process according to claim 13, wherein the hydroperoxide is tert.butylhydroperoxide.

16) A process according to claim 1, wherein the chiral complex is prepared from a chiral alcohol and titanium alkoxide.

17) A process according to claim 16, wherein the chiral alcohol is selected form esters of tartaric acids.

18) A process according to claim 17, wherein the esters are (-)-diethyl D-tartrate and (+)-diethyl L-tartrate.

19) A process according to claim 1, wherein oxidation is carried out in the presence of a base.

20) A process according to claim 19, wherein the base is an amine.

21) A process according to claim 20, wherein the amine is selected from triethylamine, diisopropylethylamine, pyridine, morpholine and N-methyl morpholine.

22) A process according to claim 1, wherein the reaction of the compound of formula III with the compound of the formula IV in step (b) is carried out in a solvent or a mixture of solvents.

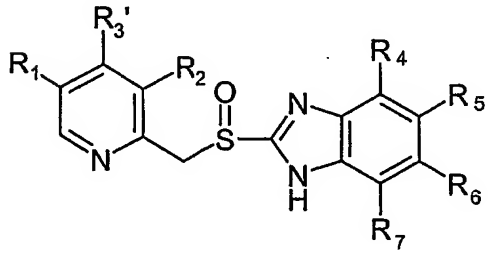
23) A process according to claim 22, wherein the solvent is selected from the group consisting of carboxylates such as ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate; alcohols such as methanol, ethanol and isopropyl alcohol; acetonitrile; tetrahydrofuran; dimethylformamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons such

as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as methylene dichloride, chloroform, carbontetrachloride, ethylene dichloride, etc.; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone etc.; ethers such as tert-butyl methyl ether, diethyl ether; and diethyl carbonate.

24) A process according to claim 23, wherein the solvents are selected from ethyl acetate, tetrahydrofuran, toluene, methyl ethyl ketone, methyl isobutyl ketone, methylene dichloride, tert-butyl methyl ether and diethyl carbonate.

25) A process according to claim 1, wherein the M is sodium or potassium.

26) A compound of the formula III either as a single enantiomer or in an enantiomerically enriched form:



---------- III

wherein

R_1 and R_2 are same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, phenylalkyl and phenylalkoxy;

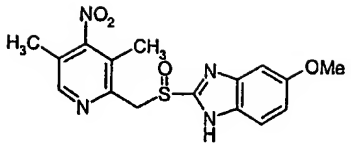
R'_3 is halo or nitro;

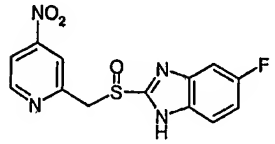
and

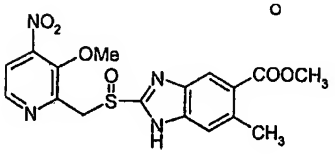
R_4, R_5, R_6 and R_7 are same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl and trifluoroalkyl.

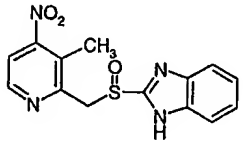
27) A compound of the formula III as defined in claim 26 either as a single enantiomer or in an enantiomerically enriched form.

28) A compound of the formula III as defined in claim 26 is selected from;


IIIa


IIIb


IIIc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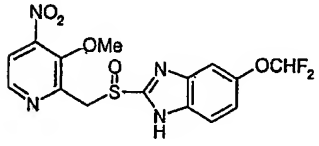
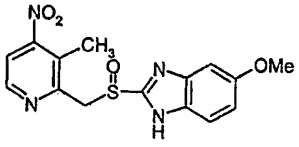

IIIe


IIIf

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2003/000384

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE: WPI, EPODOC; STN Karlsruhe: CAS: REGISTRY, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2001/004109 A1 (QUIMEICA SINTETICA, S.A.) 18 January 2001 (18.01.2001) *examples*	26-28
Y	*pages 10, 15-28 and examples*	1-25
Y	US 5948789 A (LARSON ET AL.) 7 September 1999 (07.09.1999) *columns 8-10 and examples*	1-25
X	ES 2060541 A1 (LABARATORIOS VINAS S.A.) 16 November 1994 (16.11.1994) *examples*	26-28
A	*the whole document*	1-25
X	ES 2023609 A (INKE S.A.) 16 January 1992 (16.01.1992) *the whole document*	26-28
A	*the whole document*	1-25

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
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„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2004 (27.08.2004)	3 September 2004 (03.09.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer SLABY S. Telephone No. 1/53424/348

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2003/000384

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003/097606 A1 (HERBEX, PRODUTOS QUIMICOS S.A.) 27 November 2003 (27.11.2003) *the whole document*	26-28
A	*the whole document*	1-25
X	WO 2002/028852 A1 (DINAMITE DIPHARMA) 11 April 2002 (11.04.2002) *the whole document*	26-27
A	*the whole document*	1-25,28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ıtional application No.
PCT/IN 03/00384-0

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
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ES	A	2060541	1994-11-16		none	
US	A	5948789		JP	T 10504290T	1998-04-28
				MA	A 23611	1996-04-01
				DE	T 69530987T	2004-05-19
				ES	T 2199998T	2004-03-01
				SI	T 77394OT	2004-02-29
				PT	T 77394OT	2003-10-31
WO	A	2001004109			none	
WO	A	2002028852			none	